UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/200,791 | 11/30/1998 | THOMAS M. BEHR | 018734/0161 | 9799 |

26633 7590 01/23/2006

HELLER EHRMAN WHITE & MCAULIFFE LLP
1717 RHODE ISLAND AVE, NW
WASHINGTON, DC 20036-3001

| EXAMINER | |
|---|---|
| FETTEROLF, BRANDON J | |
| ART UNIT | PAPER NUMBER |
| 1642 | |

DATE MAILED: 01/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov



# BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/200,791
Filing Date: November 30, 1998
Appellant(s): BEHR ET AL.

Patricia D. Granados
For Appellant

## EXAMINER'S ANSWER

This is in response to the appeal brief filed on 11/07/2005 appealing from the Office action mailed 09/29/2005.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

Issue 2:

Claims 1-9, 11-21, 23-29 and **31-41** are rejected under 35 U.S.C. 103(a) as being unpatentable over Behr et al (Cancer Research 55:3825-3834, 1995), and further in view of Grey et al (U. S. Patent 5,380,513, issued 1/10/95, IDS #4) and Raines et al (U.S. Patent 5,840,296, filed 10/15/97).

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

With regards to Issue 1:

-Behr et al. (Cancer Research 1995; 55: 3825-3834) ("Behr")

With regards to Issue 2:

- Behr et al. (Cancer Research 1995; 55: 3825-3834)

| | | |
|---|---|---|
| - 5,380,513 | GREY et al. | 1-1995 |
| - 5,840,296 | RAINES et al. | 10-1997 |

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-8, 11-19, 23-28, 31-39 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Behr et al (Cancer Research 55:3825-3834, 1995).

The claims recite a method of reducing kidney retention of a protein conjugate or in a patient undergoing treatment comprising administering D-lysine or poly-lysine of 15-30kD or a combination of two compounds and a protein conjugate to a patient and the protein conjugate is not greater than 60 kD, wherein the conjugate is a imaging isotope or a therapeutic isotope, wherein the solution is administered to the patient as a continuous infusion, i.v., i.p, orally, one injection or a continuous infusion, wherein the conjugate is a radiolabeled hapten conjugate. This rejection is made because the application is not grated the priority of the '899 application due to no support for the genus of proteins as indicated above and because an antibody is a protein. In addition, claim 38 is granted the priority of the instant application because of the new matter rejection and the art is

being applied to what is enabled which is a protein conjugate comprising a cytotoxic or imaging agent (see above).

Behr et al teach a method of reduction of renal uptake of a protein conjugate of an antibody fragment of Fab' of which when conjugated is less than 60kD comprising an imaging or therapeutic moiety in a patient (mouse model) with addition of D-lysine and poly-lysine (15-30 kD) and the solutions were administered by iv or ip or orally and two compounds were administered together (see entire document, especially abstract, page 3826, 3827, 3rd paragraph, 3830, left column first paragraph).

Claims 1-9, 11-21, 23-29 and 31-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Behr et al (Cancer Research 55:3825-3834, 1995), and further in view of Grey et al (U. S. Patent 5,380,513, issued 1/10/95, IDS #4) and Raines et al (U.S. Patent 5,840,296, filed 10/15/97).

Claims 1-8, 11-19, 23-28, 31-39, 41 have been described supra. Claims 9, 20-21, 29, 40, recite wherein the compound is poly-D-lysine, wherein the targeting protein conjugate is ONCONASE. This rejection is made because the application is not grated the priority of the '899 application due to no support for the genus of proteins as indicated above and because an antibody is a protein. In addition, claim 38 is granted the priority of the instant application because of the new matter rejection and the art is being applied to what is enabled which is a protein conjugate comprising a cytotoxic or imaging agent (see above).

Behr et al teach a method of reduction of renal uptake of a protein conjugate of an antibody fragment of Fab' of which when conjugated is less than 60kD comprising an imaging or therapeutic moiety in a patient (mouse model) with addition of D-lysine and poly-lysine (15-30 kD) and the solutions were administered by iv or ip or orally and two compounds were administered together

(see entire document, especially abstract, page 3826, 3827, 3rd paragraph, 3830, left column first paragraph). Behr et al does not teach a protein conjugate comprising a ribonuclease or ONCONASE. These deficiencies are made up for in the teachings of Grey et al and Raines et al.

Grey et al teach a method to reduce renal retention of protein conjugates with lysine (see abstract and column 3, lines 44 to column 4, lines 2). Grey et al teach the conjugates comprise imaging agents and therapeutic agents (see column 7), that comprise cytotoxins and the proteins comprise receptors and enzymes as well as other proteins (see columns 5-6) Grey et al also teach administration orally, iv, ip, or the like (column 6, lines 1-5).

Raines et al teach conjugates comprising ribonuclease which have been effective in tumor patients (see column 1) and the decrease in renal function of Onconase may be the consequence of an inability to effectively clear the Onconase protein from the kidneys (see column 2, lines 52-57). Onconase is a 104 amino acid protein (see column 2, lines 34-35) which is not greater than 60 kD.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Behr et al teach that kidney retention was reduced in conjugates by addition of lysine and poly-lysine and that poly-lysine (15-30 kD) was more effective in reducing renal uptake and D-lysine should be metabolically inert (see page 3829 and 3832). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable

expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Grey et al teach that protein conjugates comprising enzymes and added lysine can reduce renal uptake of the conjugates. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr et al, Grey et al, and Raines et al because Raines et al teach "A cytotoxic ribonuclease that is readily cleared from the kidneys would be less likely to cause renal toxicity" (see column 2, lines 58-62). Thus it would have been obvious to one of ordinary skill in the art to produce a method of reducing renal uptake of protein conjugates that comprise ONCONASE conjugates in view of the teachings of Behr et al, Grey et al, and Raines et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

**(10) Response to Argument**

Issue 1:

Appellant's argue that Behr does not anticipate the subject matter of Claims 1-8, 11-19, 23-28, 31-39 and 41 because Behr was published on September 1, 1995 and the rejected claims are entitled to the benefit of the filing date of USSN 08/407,899 ("the '899 application"), March 21, 1995, which is prior to September 1, 1995. As such, Appellants' submit that reliance upon and entitlement to this 1995 priority date is the primary point of dispute between Appellants' and the Examiner. For example, Appellants argue that the Examiner does not articulate a specific statutory or legal basis for his denial of priority, the Examiner simply states that "the species of antibodies

does not support the genus of just any protein conjugate." Moreover, Appellants argue that the Examiner is wrong as a matter of law, if the Examiner believes that a species can never support a genus, and is wrong as a matter of fact with regard to this case in particular. Appellants contend that the present application is a continuation-in part ("CIP") of the '899 application and that the basic rule in order for a claim in a CIP to be entitled to the filing date of an earlier application, the earlier application must comply with the requirements of 35 USC 112, first paragraph, with regard to the later claimed subject matter. Appellants further submit that determination of priority are mostly concerned with the written description requirement of 35 USC 112, first paragraph. As such, Appellants submit that in order to meet the written description requirement, the applicant must convey with reasonably clarity to those skilled in the art that, as of the filing date sought, he or she was **in possession of the invention**. Vas-Cath Inc. v. Mahurkar 935 F.2d 1555, 19 USPQ 2d 1111 (Fed. Cir. 1991) (emphasis added). Thus, Appellants assert that the adequacy of the description is judged from the viewpoint of one of ordinary skill in the art of the invention and involves questions of fact.

Secondly, Appellants submit that in a recent case, Pandrol USA, LP et al. v. Airboss Railway Products, Inc. et al. (Slip. Op. 04-1069) (September 19, 2005), the U.S. Court of Appeals for the Federal Circuit applied the law of Vas-Cath in considering whether a claim reciting "adhering material" was supported by an original description in the specification of two examples of materials that functioned as adhesive materials: an HDPE closed cell foam pad and an epoxy, wherein the court concluded that because such material were, in fact, adhering material, the written description requirement for claimed "adhering materials" was met. Hence, Appellants contend that in Pandrol, the disclosure of two species was sufficient to support the recitation of a genus. In the present case, Appellants argue that just as a foam pad was and/or *functioned* as an adhesive material in Pandrol, the

disclosed antibodies are and/or *function* as a type of protein conjugate In fact, Appellants argue that the problem solved in the '899 application using antibodies is the same problem solved by protein conjugates in the present application. Specifically, Appellants submit that the '899 application, which matured into U.S. Patent No. 5,843,894 ("the 894 patent") discloses a solution to the problem involving the renal uptake of molecules that are smaller than 60Kd, which is a particular problem with immunotherapy and immunodiagnostics where such molecules are labeled with radioisotopes. (The '894 patent at column 1, lines 33-36) Moreover, Appellants submit that the '894 patent describes how other have recognized this problem and offered other solutions, namely treatment with basic L-amino acids to reduce the uptake of radiolabelled peptides and antibody fragments. (Column 1, lines 39-50) Although the above discussion is mostly in the "Background of the Invention" part of the specification, Appellants argue that the discussion is highly relevant to the claimed invention because it defines the problems addressed by the claimed invention. More specifically, Appellants submit that it defines the universe of proteins that creates the problem solved by the invention, wherein the proteins in that universe have a certain size which causes them to be related in the kidney.

Thirdly, Appellants take issue with the Examiner's statement that "the species of antibodies does not support the genus of *just any protein conjugate.*" Supra, (Emphasis added) Appellants argue that Claims 1 and 38 are not directed to just any protein conjugate, but recite a protein conjugate having a specific molecular weight, e.g., **a molecular weight not greater than about 60kD,** which is described in the '894 patent as being filterable by the glomeruli and thereby retained in the kidney. Moreover, Appellants argue that claim 18 also recites a size limitation of the protein conjugate and further describes the conjugate as being a "targetable protein conjugate." Appellants point out that it is clear that the in the '894 patent targeting protein conjugates are antibody fragments conjugates

with radioisotopes or cytotoxic agents, while the proteins of the present application could be antibody fragments or any other protein conjugate of a specific size that is retained in the kidney. Therefore, Appellants submit that one of ordinary skill in the art of the invention, knowing that antibody conjugates are protein conjugates and that the method described in the '899 application is the same method, for the same purpose as the method described in the present application, would understand that Appellants were in possession of the claimed invention at the time of the filing of the '899 application.

Fourthly, with regards to claims 2 and 19, which recite specific types of protein conjugates, Appellants argue that the above analysis is applicable. That is, Appellants have included peptide conjugates, polypeptide conjugates, glycoprotein conjugates, lipoprotein conjugates, antibody conjugates and antibody fragment conjugates in the same Markush claim because each member is a type of protein conjugate.

These arguments have been carefully considered, but are not found persuasive.

With regards to Appellants argument that the Examiner does not articulate a specific statutory or legal basis for his denial of priority and the Examiners believes that a species can never support a genus, the Examiner recognizes that disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the genus. *See* MPEP 2163 II A 2 (a) (ii) (emphasis added). In this case, as set forth in the previous Non Final Office Action (10/21/2004, page 3), "[C]laims 1 and 18 in the instant application recite the limitation of a method of reducing kidney retention of a protein conjugate. This limitation is not seen in the 08/407899 application. The 08/407899 application is directed to reducing renal uptake of antibody and antibody fragment conjugates which is a species of the now claimed genus of protein conjugates. The species of

antibodies does not support the genus of just any protein conjugate." With regards to Appellants contention in order for a claim in a continuation-in part ("CIP") to be entitled to the filing date of an earlier application it must comply with the requirements of 35 USC 112, first paragraph, with regard to the later claimed subject matter, the Examiner agrees with Appellants contention that in order to meet the written description requirement, the "applicant" must convey with reasonably clarity to those skilled in the art that, as of the filing date sought, he or she was **in possession of the invention**. Vas-Cath Inc. v. Mahurkar 935 F.2d 1555, 19 USPQ 2d 1111 (Fed. Cir. 1991) (emphasis added). However, as set forth in the Advisory Action (9/29/2005, page 2-3), "[T]he instant application was given a priority date of 11/30/1998 because the '894 patent, directed to reducing renal uptake of an antibody and antibody fragment conjugates, does not appear to contemplate or suggest a method of reducing renal uptake of the presently claimed genus of protein conjugates. As such, it does not appear that those of skilled in the art would reasonably convey that Appellants were in possession of instantly claimed genus." In reference to Vas-Cath Inc. v. Mahukar, it appears that the fact patterns involved in the instant application are different from those concerned in Vas-Cath Inc. v. Mahukar. In Vas-Cath Inc. v. Mahukar, the question decided by the courts was whether the drawings recited in the prior application conveyed with reasonable clarity to those of ordinary skill that Mahurkar had in fact invented the catheter recited in the those claims, having (among several other limitation) a return lumen diameter substantially less than 1.0 but substantially greater than 0.5 times the diameter of the combined lumens. In the instant application, the question is not whether the drawings (i.e. design patent) provided a written description of the claimed genus of protein conjugates (i.e,. utility patent), but instead, whether the disclosure of one species in the '894 patent is sufficient to described the entire genus as presently claimed. As discussed supra, the '894

patent does not reasonably convey to those skilled in the art that applicants at the time of the invention were in possession of the claimed genus of protein conjugates.

With regards to Appellants second argument pertaining to the courts conclusion in Pandrol USA, LP et al. v. Airboss Railway Products, Inc. et al. (Slip. Op. 04-1069) (September 19, 2005), the Examiner agrees with the courts application of Vas-Cath in determining that a claim reciting "adhering material" was supported by an original description in the specification of two examples of material that function as adhesive materials. However, it appears that the fact patterns involved in the instant application are different from those concerned in Pandrol USA, LP et al. v. Airboss Railway Products, Inc et al.. In Pandrol USA, LP et al. v. Airboss Railway Products, Inc et al., for the purposes of written description analysis, the court's focus is on the original disclosure.

> The specification discloses that the invention provides an effective adhesive seal between the plate and the concrete tie ('046 patent, col. 2, II. 6-10).
> The original specification states:
>> Preferably the abrasion plate may be adhered to the surface of the concrete tie to ensure that ingress of abrasive particles and water onto the surface of the rail tie is avoided. (at col. 2, II. 7-10)
> The original specification also states:
>> The plate 10 may be bonded by adhesive (epoxy resin adhesives are preferred) to the tie 1 or an HDPE closed cell foam of 1.5 mm thickness of the same size and shape as plate 10 is fitted between plate 10 and 1. (Specification of the '046 patent at 4)

In the instant application, the original specification in the parent application does not appear to expressly disclose a "protein conjugate" as claimed in the instant application. Furthermore, the original specification in the parent application only appears to be directed to reducing renal uptake of an antibody and antibody fragment conjugates. As such, the original specification of the '894 patent does not reasonably convey to those skilled in the art that applicants at the time of the invention were in possession of the claimed genus of protein conjugates as of the filing date of the '899 application.

With regards to Appellants issue with the Examiner's statement that "the species of antibodies does not support the genus of *just any protein conjugate*", the Examiner agrees with Appellants argument that Claims 1, 18 and 38 are not directed to just any protein conjugate, but recite a protein conjugate, wherein the protein conjugate has a specific molecular weight, e.g., **a molecular weight not greater than about 60kD**; and further, that the Background of the Invention of the '894 patent recites how the renal uptake of proteins smaller than 60kD occur. However, there does not appear to be any contemplation other than antibody fragments as the "protein conjugates". In fact, as stated in the Final Rejection (06/07/2005, page 4), the '894 patent teaches "[T]his invention relates to a method for reducing renal uptake of monoclonal antibody fragments" (see column 1, lines 1-6) Moreover, the recitation of "[R]enal uptake of peptides and small protein is though to occur via glomerular filtaion of molecules smaller than 60Kd" in the '894 patent only appears to serve as a review of the prior art rather than to describe the invention claimed in the present application.

In response to Appellants arguments pertaining to claims 2 and 19, which recite specific types of protein conjugates, the Examiner recognizes that Appellants have included peptide conjugates, polypeptide conjugates, glycoprotein conjugates, lipoprotein conjugates, antibody conjugates and antibody fragment conjugates in the same Markush claim. However, for the reasons set forth above, glycoprotein conjugate and lipoprotein conjugates do not appear to have support in the 08/407, 899 application.

Therefore, the claims are not grated the priority date of the '894 application and as such, the rejection stands.

Issue 2:

Appellants reiterate the above arguments with regard to the Examiner's rejection under 35 U.S.C. 102 (b) and add that the secondary references cannot sustain an obviousness rejection without Behr.

This argument has been carefully considered, but is not found persuasive.

In response to this argument, the claims are not grated the priority date of the '894 application and as such, the rejection stands.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Brandon Fetterolf, Ph.D.

Conferees:

Jeff Siew, J.D

Larry Helms, Ph.D

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
1/19/06

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER
1/20/06 Conferee